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Original Article

Effect of endovascular therapy on the expression levels of serum T lymphocyte subsets, Notch1 and TACE proteins in patients with abdominal aortic aneurysm

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Abstract: To investigate the effect of endovascular therapy on the expression levels of serum T lymphocyte subsets, Notch1 and TACE proteins in patients with abdominal aortic aneurysm (AAA). A total of 84 AAA patients treated in the General Hospital of Northern Theater Command of Chinese PLA from January 2018 to October 2019 were equally divided into the control group and research group according to different surgical methods. The control group underwent laparotomy and the research group received endoluminal repair. The expression levels of serum T-cell subsets, plasma Notch1 and TACE proteins were compared before and 1 week after surgery between the two groups; the expression levels of plasma Notch1 and TACE proteins in patients with different tumor diameters in the research group were compared; the comparison of the surgical indexes and the incidence of complications was conducted. After treatment, the molecular level of $CD3^+$ and $CD4^+$ in the research group was significantly higher than that in the control group, whereas the molecular level of $CD8^+$, and the expression levels of Notch1 and TACE proteins in the plasma were significantly lower than that in the control group ($P < 0.05$). In the research group, the expression levels of plasma Notch1 and TACE proteins were in direct proportion with tumor diameter ($P < 0.05$). The intraoperative blood loss in the research group was significantly less than that in the control group, the operation time, postoperative fasting time and postoperative hospital stay were significantly shorter than that in the control group, and the total incidence of complications (11.90%) was significantly lower than that in the control group (38.09%) ($P < 0.05$). At 12 months after operation, there was no statistically significant difference in the incidence of complications and mortality between the two groups. Endovascular therapy fro AAA can greatly improve the expression levels of T-lymphocyte subsets, Notch1 and TACE proteins, and markedly reduce the incidence of complications.

Keywords: Endoluminal therapy, abdominal aortic aneurysm, serum T lymphocyte subsets, Notch1 protein, TACE protein

Introduction

Abdominal aortic aneurysm (AAA) is an aneurysm-like dilation of the abdominal aorta exceeding the normal diameter by more than 50% of its original size, which often occurs in elderly men [1]. This disease is characterized by dilatation of the abdominal aortic wall, which in severe cases can lead to rupture, thereby causing massive hemorrhage and can be life-threatening. The risk of aneurysm rupture is markedly increased, especially in smokers. In recent years, with the continuous improvement of people's living standards, the increasing aging population and the continual progress of medical technology, the incidence of AAA has been increasing annually, and AAA is the most common type of all aneurysms [2].

The body normally requires the coordination of lymphoid organs and lymphocytes to maintain normal immune function. Tumor site cause an inflammatory response, which in turn affects the body's and T-lymphocytes' recognition and clearance of cancer cells, leading to an immune disorder. Detection of plasma T lymphocytes

can reflect the cellular immune function of the body [3]. Notch1 and TACE proteins are important components of the Notch signaling pathway. Moreover, TACE shows a high expression level in AAA under activated Notch1 protein [4]. Therefore, it is necessary to adopt safe and effective means to treat AAA so as to avoid tumor rupture which endangers the patient's life. The primary aim of our study was to investigate the effect of endovascular therapy on the expression levels of serum T lymphocyte subsets, Notch1 and TACE proteins in patients with AAA.

Materials and methods

General data

Patients with AAA who were admitted to the General Hospital of Northern Theater Command of Chinese PLA from January 2018 to October 2019 were selected. Inclusion criteria: (1) patients confirmed with AAA by abdominal aortic B ultrasound, CT and other imaging examinations; (2) patients with vascular sclerosis around the abdominal aortic aneurysm; (3) patients with abdominal aortic morphology of true aneurysm, shuttle, $r \geq 5$ cm; (4) patients who received treatment for the first time. Exclusion criteria: (1) patients with saccular aneurysms or infective aneurysms; (2) patients with deep vein thrombosis of the lower extremities; (3) patients with severe stenosis or lesions in the peripheral arteries; (4) patients complicated with heart, liver and kidney dysfunction or other serious systemic organic diseases. Eighty-four patients were eventually included, all of whom voluntarily signed an informed consent form and the experiments performed in this study were approved by the Ethics Committee of General Hospital of Northern Theater Command of Chinese PLA.

Patients were divided into the control group (n = 42) and research group (n = 42) according to different surgical methods. In the control group, there were 27 males and 15 females, aged 50-75 years (mean: 63.27 ± 5.64 years); the mean tumor diameter was (6.23 ± 0.54) cm; complications: hyperlipidemia in 6 cases, diabetes in 9 cases, hypertension in 23 cases, and chronic obstructive pulmonary disease in 4 cases. In the research group, there were 28 males and 14 females, aged 51-76 years (mean: 62.53 ± 5.75 years); the mean tumor diameter was (6.46 ± 0.39) cm; complications: hyperlipidemia in 4 cases, diabetes in 11 cases, hypertension in 22 cases, and chronic obstructive pulmonary disease in 5 cases. No statistically significant difference was observed in the general data (gender, age, tumor size, etc.) of patients between the two groups ($P > 0.05$).

Methods

In the control group, laparotomy was carried out. After total anesthesia, a midline incision was made as a vertical cut in the abdomen to cut the peritoneum, and then expose the aortic aneurysm, left renal artery and bilateral iliac arteries. Afterwards, the aneurysm neck was isolated, and 5,000 U of heparin was injected into the aortic aneurysm for heparin treatment; the aortic artery and iliac artery were isolated at the proximal and distal positions of the aneurysm so that the forearm of the aneurysm was cut off to remove the sclerotic plaque and thrombus and suture. The bifurcated or straight artificial vessel was taken for grafting and the reconstruction of the abdominal aorta. After blood flow was restored, the aneurysm wall was wrapped so that the artificial vessel was implanted, the peritoneum was sutured, and the abdominal incision was closed.

In the research group, endoluminal repair was performed. After total anesthesia, the bilateral femoral arteries were exposed and abdominal aortic angiography was performed to ensure the feasibility of endoluminal repair. Next, 5000 U of heparin was injected into the abdominal aortic aneurysm for heparin treatment. Later, the femoral artery on one side was cut to observe the shape and size of the aneurysm. A suitable coating stent was used and placed into the abdominal aorta under the dynamic monitoring of angiography to ensure that the stent was positioned at the proximal and distal ends of the aortic aneurysm. Afterwards, the aneurysm wall was isolated and the blood flow in the stent was ensured to be smooth, and then the low-pressure dilatation balloon was gradually released in a correct way. Blood flow in the abdominal aorta was again observed, and the femoral artery was repaired after it was determined that there was no internal leakage.

The peripheral blood mononuclear cells (PBMC) of the two groups were prepared using flow cytometry (FACSAria III type from American BD company). ① Three tubes of PBMC with a con-

centration of 1×10^{10}/L were taken from the two groups, each with 100 ml, anti-CD3-FITC, anti-CD4-FITC and anti-CD8-FITC flow cytometry fluorescently labeled antibodies, we added, each with 20 μl; ② Solution was mixed well, incubated at 25°C for 30 min in the dark, then centrifuged at 2000 r/min for 10 min at 4°C, discard of the supernatant, and 500 μl of phosphate buffered saline (PBS) buffer was added to the pellet and rinsed gently to remove excess unbound antibody, and the solution was centrifuged again with a 4°C centrifuge at 2000 r/min for 10 min, this was repeated twice; ③ Solution was placed in the machine with 400 μl PBS buffer, with adjustment of the flow cytometer to the best working state, and application of anti-CD3-FITC, anti-CD4-FITC and anti-CD8-FITC flow cytometry fluorescent labels respectively for the two groups of PBMC, and detection of the percentage of $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes.

Outcome measures

(1) The comparison of the expression levels of T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$), plasma Notch1 and TACE proteins before treatment and one week after treatment was carried out in the two groups. (2) The expression of Notch1 protein was compared with that of TACE protein in the plasma of patients with different tumor diameters in the research group. (3) The comparison of the surgical indexes (operation time, intraoperative blood loss, postoperative fasting time, and postoperative hospital stay) and the incidence of complications (infection, water and electrolyte disorders, digestive system and pulmonary diseases) was conducted in the two groups.

A total of 5 mL of venous blood was collected from the patients under fasted conditions in the morning before surgery and one week after surgery, it was centrifuged at 1500 r/min for 10 min (r = 15 cm) to obtain 100 μL of serum. Later, it was placed in an EP tube and stored at -20°C for future examination. Serum T lymphocyte ($CD3^+$, $CD4^+$, $CD8^+$) levels were measured by automatic flow cytometry; Notch1 and TACE protein levels in plasma were detected by enzyme-linked immunosorbent assay (ELISA) kit (CUSABIO).

Follow-up

Patients were reviewed every 3 months after surgery, and the follow-up time was up to 12 months. Patients who withdrew from the study were excluded.

The incidence of complications and mortality in patients at 12 months after surgery were counted, and the deaths at 3 months, 6 months and 12 months after surgery were counted.

Statistical analysis

SPSS 19.0 statistical software was used to analyze the data. The quantitative data were expressed as $\bar{x} \pm sd$, and analyzed by t test, multi-group comparisons were undertaken by the analysis of variance; the qualitative data were presented as n (%), and analyzed by chi-square test and Fisher exact test; GraphPad Prism 8 was used to illustrate the data. $P < 0.05$ was regarded as statistically significant.

Results

Comparison of T lymphocytes subsets before and after treatment between the two groups

After treatment, $CD3^+$ and $CD4^+$ molecule levels were remarkably increased, but $CD8^+$ was remarkably decreased in both groups; $CD3^+$ and $CD4^+$ molecule levels were markedly higher, but $CD8^+$ was markedly lower in the research group than in the control group, and the differences were statistically significant ($P < 0.05$) (**Table 1**; **Figures 1**, **2**).

Comparison of the expression levels of plasma Notch1 and TACE proteins between the two groups

Before treatment, there was no statistical significance in the expression levels of plasma Notch1 and TACE proteins between the control group and research group ($P > 0.05$); after treatment, the expression levels of plasma Notch1 and TACE proteins in the control group were decreased, but they were still significantly higher than those in the research group ($P > 0.05$); the expression levels of plasma Notch1 and TACE proteins in the research group were markedly reduced, and were lower than those before treatment ($P < 0.05$) (**Table 2**).

Expression levels of Notch1 and TACE proteins in the plasma of patients with different tumor diameters in the research group

The expression levels of plasma Notch1 and TACE proteins were remarkably higher in

Table 1. Comparison of T lymphocytes subsets before and after treatment between the two groups ($\bar{x} \pm sd$)

Group	n	$CD3^+$ (%)		$CD4^+$ (%)		$CD8^+$ (%)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	42	28.14 ± 3.17	35.43 ± 4.56	24.84 ± 3.41	35.37 ± 4.59	24.36 ± 2.58	19.44 ± 3.27
Research group	42	28.35 ± 3.06	42.18 ± 4.25	25.19 ± 3.12	43.29 ± 5.14	23.97 ± 2.83	14.26 ± 3.15
t		0.308	7.018	0.490	7.448	0.660	7.394
P		0.758	< 0.001	0.624	< 0.001	0.511	< 0.001

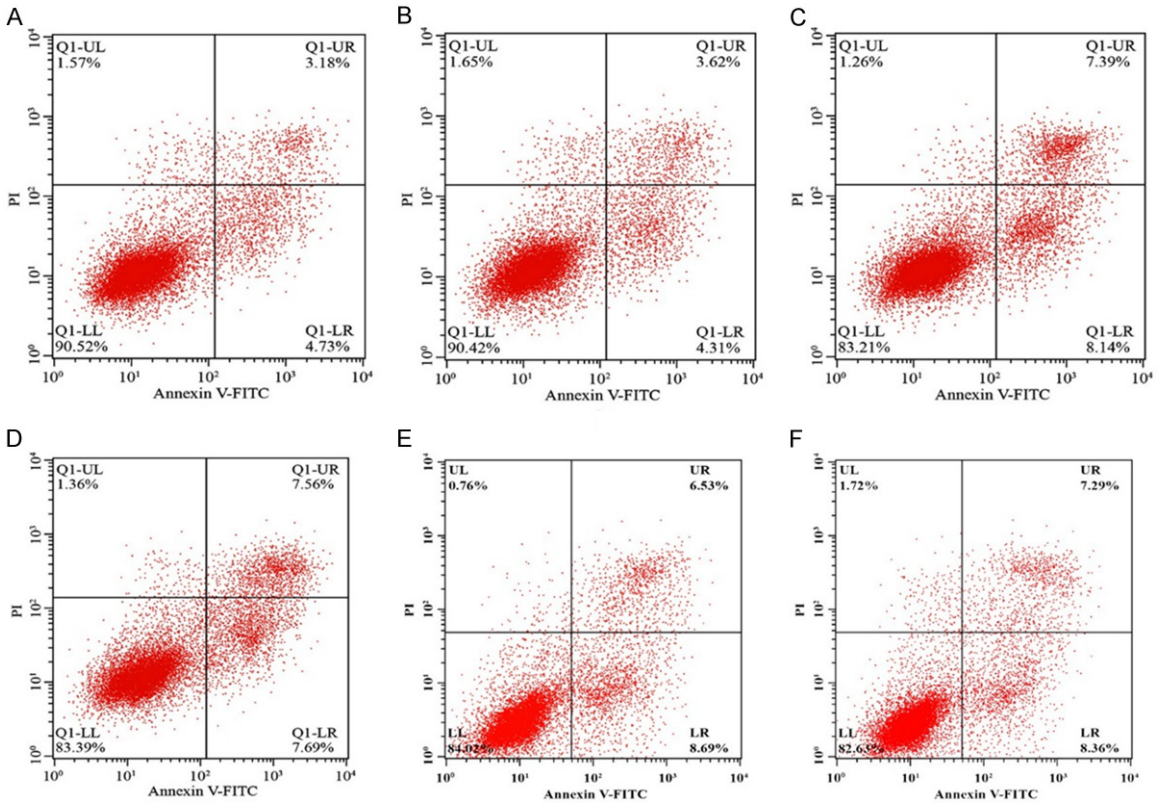

Figure 1. Cell condition detected by flow cytometry before treatment. Note: A. Control group $CD3^+$ Pre-treatment; B. Research group $CD3^+$ Pre-treatment; C. Control group $CD4^+$ Pre-treatment; D. Research group $CD4^+$ Pre-treatment; E. Control group $CD8^+$ Pre-treatment; F. Research group $CD8^+$ Pre-treatment.

patients with tumor diameters of 5-7 cm than in patients with diameters of < 5 cm (P < 0.05). The expression levels of plasma Notch1 and TACE proteins were remarkably higher in patients with tumor diameters of > 7 cm than in patients with diameters of < 5 cm and 5-7 cm (P < 0.05) (**Table 3**).

Comparison of the indicator of surgical treatment between the two groups

During treatment, the intraoperative blood loss in the research group was significantly less than that in the control group, and the operation time, postoperative fasting time and postoperative hospital stay were significantly shorter than that in the control group, there was a statistically significant difference (P < 0.05) (**Table 4**).

Comparison of the incidence of postoperative complications between the two groups

The total incidence of complications (11.90%) was remarkably lower in the research group than that in the control group (38.09%), with a difference that was statistically significant (P < 0.05), as shown in **Table 5**.

Follow-up results

All patients in both groups were followed up. At 12 months after operation, there was no statis-

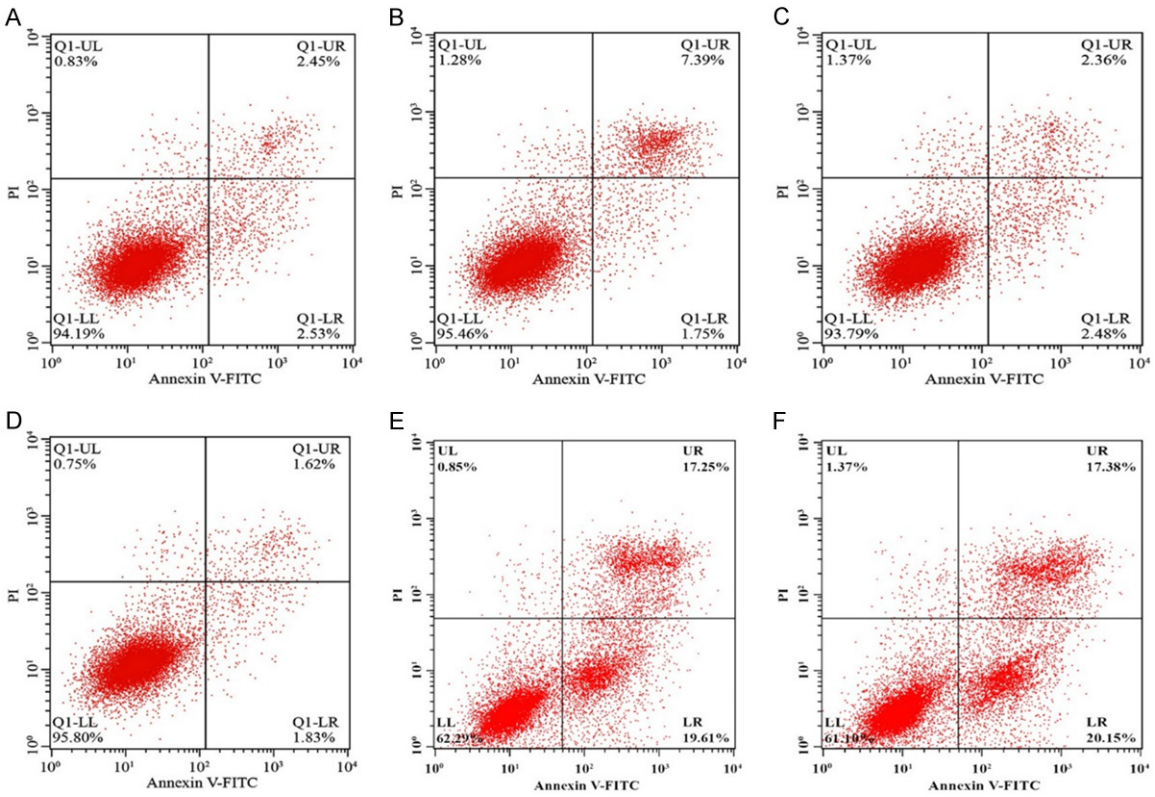

Figure 2. Cell condition detected by flow cytometry after treatment. Note: A. Control group $CD3^+$ Post-treatment; B. Research group $CD3^+$ Post-treatment; C. Control group $CD4^+$ Post-treatment; D. Research group $CD4^+$ Post-treatment; E. Control group $CD8^+$ Post-treatment; F. Research group $CD8^+$ Post-treatment.

Table 2. Comparison of the expression levels of plasma Notch1 and TACE proteins between the two groups

Group	n	Notch1 protein ($pg{\cdot}mL^{-1}$)		TACE protein ($pg{\cdot}mL^{-1}$)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	42	181.67 ± 20.95	153.28 ± 19.43	2324.57 ± 210.83	1947.56 ± 193.48
Research group	42	183.42 ± 21.57	124.58 ± 17.64	2317.26 ± 214.35	1489.43 ± 184.57
t		0.377	7.088	0.157	11.100
P		0.707	< 0.001	0.875	< 0.001

Table 3. Comparison of the expression levels of Notch1 and TACE proteins in the plasma of patients with different tumor diameters in the research group

Tumor diameter	n	Notch1 protein ($pg{\cdot}mL^{-1}$)	TACE protein ($pg{\cdot}mL^{-1}$)
< 5 cm	11	162.34 ± 19.57	1985.36 ± 194.16
5-7 cm	18	176.28 ± 21.45	2213.47 ± 205.34
> 7 cm	13	216.53 ± 23.84	2673.28 ± 264.52
F		21.050	30.610
P		< 0.001	< 0.001

tically significant difference in the incidence of complications and mortality between the two groups of patients (P > 0.05), as shown in **Tables 6**, **7**. Deaths of the two groups of patients at 3, 6 and 12 months after operation were shown in **Table 7**.

Discussion

Abdominal aortic aneurysm (AAA) is more common in clinical vascular surgery, mainly manifesting as atherosclerosis, with most patients having no obvious symptoms, and a few having only a feeling of pressure. It commonly presents as upper abdominal fullness and discomfort [5]. Medical staff has been intensively studying the effective treatment means for this disease, but the mainstay of treatment is still

Table 4. Comparison of intraoperative and postoperative index values between the two groups ($\bar{x} \pm sd$)

Group	n	Operation time (min)	Intraoperative blood loss (mL)	Postoperative fasting time (d)	Postoperative hospital stay (d)
Control group	42	294.36 ± 47.28	396.54 ± 58.32	4.78 ± 2.54	16.25 ± 3.58
Research group	42	225.18 ± 32.64	153.48 ± 23.17	1.85 ± 0.36	9.34 ± 2.63
t		7.804	25.100	7.402	10.080
P		< 0.001	< 0.001	< 0.001	< 0.001

Table 5. Comparison of the incidence of postoperative complications between the two groups [n (%)]

Group	n	Infections	Water and electrolyte disorders	Digestive system	Pulmonary diseases	Overall incidence
Control group	42	4 (9.52)	4 (9.52)	3 (7.15)	5 (11.90)	16 (38.09)
Research group	42	1 (2.38)	1 (2.38)	2 (4.76)	1 (2.38)	5 (11.90)
χ^2						7.683
P						0.006

Table 6. Comparison of the incidence of complications between the two groups after 12 months

Complications	Control group (n = 42)	Research group (n = 42)	Fisher	P
Relapse	1	0	0.999	> 0.05
Endoleak	0	1		
Slight damage of covered stent	1	1		
stents shifting	0	0		
total number (%)	2 (4.76)	2 (4.76)		

surgical intervention. Conventional laparotomy is the first surgical procedure applied to AAA and it has become an established and effective treatment, but it is invasive, has a high complication rate, and is not applicable to patients with comorbidities [6]. Endoluminal repair is less invasive and has fewer complications; this procedure involves the implantation of a folded artificial vascular stent into the abdominal aortic cavity as a means of establishing a new blood flow pathway, which can be effective in preventing the aneurysm wall and the artificial vessel from being mechanized and secondary thrombosis, thus preventing enlargement or rupture of AAA [7]. In this study, patients with patients were treated with the above two modalities. The results showed the intraoperative blood loss in the research group was significantly less than that in the control group, and the operation time, postoperative fasting time and postoperative hospital stay were significantly shorter than that in the control group, and there was a statistically significant difference ($P < 0.05$). This illustrated that compared with traditional laparotomy, endoluminal repair is less traumatic to the tissues around the lesion and can markedly reduce the amount of trauma to important organs or blood vessels. Therefore, the patients in the research group recovered rapidly after surgery and had better results than those in the control group. Additionally, the total incidence of complications (infection, water and electrolyte disorders, digestive system and pulmonary diseases) (11.90%) was remarkably lower in the research group than that in the control group (38.09%), with a significant difference ($P < 0.05$). It was seen that since only slight harm to the patient's body occurs when endoluminal repair is performed, the patient can recover quickly after the surgery. As a consequence, it effectively reduces the incidence of adverse reactions, promotes blood circulation, lowers the incidence of thrombosis, and restores their gastrointestinal function.

T cells subsets in serum, including $CD3^+$, $CD4^+$, $CD8^+$ T lymphocytes and T regulatory cells, have immune killing, immunosuppressive and immune helper functions [8]. Normally, the level and function of T-cell subsets in serum are in a dynamic equilibrium, maintaining the sta-

Table 7. Comparison of deaths between the two groups at 3, 6 and 12 months after operation and the mortality rate at 12 months after operation

Groups	n	3 months after surgery	6 months after surgery	12 months after surgery
Control group	42	0	1 (2.38%)	2 (4.76)
Research group	42	0	0	1 (2.38%)
Fisher				6.348
P				0.616

bility of immune cytokines and immune function of the body while correctly exhibiting the immune activity and function of T-lymphocytes in the body, thus indirectly reflecting the recovery of the body after surgical treatment [9, 10]. Our study demonstrated that when patients developed AAA lesions, the expression of serum T cell subsets shows a trend change, the immune function of the body shows an inhibitory expression, the expression levels of $CD3^+$ and $CD4^+$ show a decreasing trend, the expression level of $CD8^+$ show an increasing trend, and a larger tumor diameter represents a more obvious change in the expression level of T cell subsets. After treatment, $CD3^+$ and $CD4^+$ molecule levels in the two groups were significantly higher than those before treatment, while $CD8^+$ was lower than that before treatment; $CD3^+$ and $CD4^+$ molecule levels in the research group were significantly higher than those in the control group, while $CD8^+$ was significantly lower than that in the control group. These results revealed that the immunity of the patient is related to the lesion, and the immune activity and function of the T lymphocyte subsets of the patients in the research group were greatly better than those in the control group after endoluminal repair, and the immunity of the body was enhanced after surgery, which can effectively accelerate postoperative recovery [11].

AAA is characterized by atherosclerosis. Studies have confirmed that the Notch signaling pathway plays a crucial role in the inflammatory response of the arterial wall and the occurrence and progression of atherosclerosis [12]. As a consequence, it is speculated that there is a certain correlation of AAA with the Notch signaling pathway. The vital components of the Notch signaling pathway are thought to be Notch1 and TACE proteins that are crucial to the occurrence and progression of AAA. In light of the fasting plasma levels in patients before treatment in this study, the serum levels of Notch1 and TACE proteins in AAA patients had a tendency to increase, indicating that the malignancy of the disease is associated with the increased levels of Notch1 and TACE proteins [13, 14]. More often than not, Notch1 on the cell surface binds to ligands on the surface of its neighboring cells and exhibits cut points for extracellular proteases. Furthermore, it is cleaved and released extracellularly by the action of TACE proteins [15, 16]. Under the effect of activated Notch1 proteins, the membrane potential of macrophages has the potential to change, which in turn polarizes and promotes the occurrence and progression of AAA [17]. For instance, under the action of activated Notch1, the membrane potential of macrophages M1 and M2 changes, resulting in a polarization response, and the inflammatory response induced by macrophages plays a certain role in promoting the development of AAA. Notch1 protein has been shown to effectively reduce the occurrence and progression of angiotensin II-induced AAA in ApoE mice, inhibit tumor metastasis and macrophage proliferation and differentiation. Besides, TACE protein level will be significantly decreased by endoluminal repair, thus markedly reducing the ability to express adhesion molecules and inflammatory factors, and further reducing the destruction of normal cellular tissue [18, 19]. Matrix metalloproteinase inhibitors are also found to show an inhibitory effect of TACE bioactivity, thus effectively the reducing inflammatory response in AAA patients [20]. Matrix metalloproteinase inhibitors have a certain inhibitory effect on the biological activity of TACE, which in turn promotes the reduction of AAA inflammation. In the present study, the expression levels of plasma Notch1 and TACE proteins were significantly decreased after surgical treatment, and the reduction was more significant in the research group than in the control group ($P < 0.05$). Interestingly, the expression levels of plasma Notch1 and TACE proteins were significantly higher in patients with tumor diameters of > 7 cm than in those with diameters of < 5 cm and 5-7 cm ($P < 0.05$), which indicated that the tumor diameters of AAA patients were positively correlated with Notch1 and TACE protein levels, and the larger tumor diameter indicated the higher expression levels

of Notch1 and TACE proteins in the patient. This is a good indication that monitoring the Notch signaling pathway during AAA formation may be a preventative factor of over-development of the tumor. After intracavitary treatment, the expression level of Notch1 and TACE protein in the patient's body was significantly lower than before treatment, suggesting that the Notch signaling pathway plays an important role in the formation of AAA. At 12 months after operation, there was no statistically significant difference in the incidence of complications and mortality between the two groups of patients. However, at 12 months after operation, 3 patients in the control group died and 1 patient in the study group died. The rapid balloon occlusion technology can quickly and effectively reduce the amount of bleeding during the operation, prevent the patient from going into hemorrhagic shock, ensure the blood perfusion of internal organs and other organs during the operation, and the trauma of the intracavitary operation is small. The small area in contact with the external environment reduces the incidence of pulmonary complications in patients; patients have less blood loss and are less prone to electrolyte disorders.

In conclusion, endovascular therapy for AAA can greatly improve the expression levels of T-lymphocyte subsets, Notch1 and TACE proteins, and markedly reduces the incidence of complications, with significant efficacy and rapid recovery.

Disclosure of conflict of interest

None.

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